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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/781,023	02/09/2001	Neil H. Riordan	RIORD.006A	1580

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EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 11/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/781,023	RIORDAN, NEIL H.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2002 and 13 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 70-79* is/are pending in the application.

4a) Of the above claim(s) *35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34 and 70-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Misook Yu.

Election/Restrictions

The prosecution history indicates that the examiner in the Office Action mailed on 10/30/01 restricted the claims of the instant application into two groups, i.e. group I, claims 1-34, drawn to a method of treating cancer and cachexia in a mammal using ***urine isolate*** and group II, claims 35 and now cancelled claims 37-69, drawn to a method of treating cachexia using ***antigen presenting cells***. Applicant's election without traverse of group 1 in Paper No. 6 is acknowledged. Claim 35 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

This examiner notes that applicant added claims 70-79 after the Restriction Requirement mailed on 10/30/2001. Claims 70-79 are drawn to a method of cancer treatment using urine isolate and APCs treated with urine isolate. Since the specification at page 1 lines 9 and 10 says that the invention is directed at inducing immune response with urine isolate alone or with antigen presenting cells which have been co-cultured with isolate of autologous urine, claims 70-79 will be examined with claims 1-34. Claims 1-35, and 70-79 are pending and claims 1-34, and 70-79 are examined on merits.

New Grounds of Rejections and Objections

Specification

The amendment filed on 8-27-2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: applicant says support for

the added specification is found in claims 18, 19, 33, and 34, but claims 18, 19, 33 do not have support for BCG. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-34, 70-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 20 recite "an effective amount of urine isolate" but it is not clear what the metes and bounds are for the phrase. The specification does not teach an effective amount of urine isolate to accomplish the purpose stated in preambles of claims 1 and 20.

Claim 20 recites "sterile urine isolate" but it is not clear what the metes and bound are for the phrase. What is the difference between the urine isolate in claim 1 and the sterile urine isolate in claim 20. The specification does not teach method of sterilization of the urine isolate.

Claim 70 recites "an effective amount" but it is not clear what the metes and bounds are for the phrase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed invention. Claims 70-79 are

drawn to cancer vaccination using a genus of antigen-presenting cells (APCs). The specification provides evidence for dentritic cells as APCs. Based on only one species, i.e. dendritic cells, one cannot predict the additional types of APCs. Since the genus includes a large number of unpredictable species, possession of one species is not seen as sufficient to reasonably convey possession of the entire genus. It is concluded that applicant adequately describes dendritic cells.

Claims 1-19 and 70-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to **enable** one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to cancer treatment, where claims 1-19 use various sizes (anything bigger that 1,000 daltons) of autlogous urine isolate from cancer patients, where claims 70-79 use the urine isolate plus APCs that have been treated with the urine isolate. Since the first paragraph of the specification says that the instant invention is directed to "inducing an immune response toward tumor" and the specification in numerous places, for example at page 13 line 5 says about "protein" in cancer a patient's own urine, the claims are interpreted as drawn to method of cancer treatment using autologous urine-derived protein vaccination.

The following is the summary of the specification:

1) At Example 7, the isolated autologous DC was incubated with the autologous urine isolate, and then the autologous urine isolate incubated DCs were intravenously reinfused into the cachexic patient with prostate cancer.
2) At Example 9, tumor of the 14 year old patient with intracranial neuroblastoma who received dendritic cells pulsed with antologous urine antigens, shrank quite a lot.
3) At Examples 10, cervical and supraclavicular adenopathy of patients with renal cell carcinoma was resolved after the twelve week injections of autologous urine isolate incubated DCs and exosomes.

4) At Example 11, the mediastinal metastases and bone metastasis of patient with renal carcinama was resolved after 4 weekly injections of dendritic cells and exosomes.
5) At Examples 12 and 13, tumors of breast cancer patients who received dendritic cells pulsed with autologous urine isolate and exosomes also shrank quite a lot.
6) At Examples 14, tumor of ureteral carcinoma patient who received dendritic cells and exosomes also shrank.
7) At Example 15, tumor of rectal carcinoma patient also shrank after the patient received dendritic cells treated with autologous urine isolate and exosomes.
8) Examples 16-18 say that cachexia in a patient with AIDS; sarcoma, or lymphoma can be treated with dendritic cells pulsed with HIU (high molecular isolate of urine), the HIU alone, or exosomes but Examples 16-18 do not say cachexia was improved or cancer was treated.

One cannot extrapolate the teachings of the specification to the claimed invention because the specification does not teach method of cancer treatment using the methods of claims 1-19 and 70-79. As the specification summary above indicates, the instant specification gives several anecdotal examples of cancer status being improved. Although it is documented in the art that malignant tumors, especially renal carcinoma disappear spontaneously, note Eldor (1997, Medical Hypothesis vol. 48, pages 309-315) at page 312 left column, the second last paragraph from bottom, this kind of miracle does not occur quite often and unpredictable. It is well recognized, however, in the art that cancer treatment is not a trivial matter. Method of cancer treatment protocol involving human subject requires undue experimentation, i.e., extensive experiments involving pre-clinical and clinical trial to determine the effective dosage. Note Table 1 at page 8515 of Griger et al (2001, Cancer Research vol. 61, pages 8513-8519) for evidence of such undue experimentatiion. The specification neither teaches any effective dose of autologous urine isolate to accomplish the purpose stated in the

preamble of the claims nor any effective dose of the urine isolate plus the treated APCs for the purpose stated in the preamble of the claims. As summarized above, all of the examples in the instant specification use dendritic cells pulsed with autologous urine isolate of unspecified sizes. In addition, the specification does not teach what is the effective dose of the APCs used. Compare the anecdotal examples of the instant specification with the dose range presented in Table 1 of Griger et al (cited supra). Therefore one cannot extrapolate the teaching of the specification to the claimed invention without undue experimentation because the specification provides no exemplification of or guidance on how to use the claimed urine isolate as immunogens for active immunotherapy in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph). In addition, Spitler (Cancer Biotherapy, 1995, 10: 1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: cancer vaccines don't work. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

Moreover, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para of column 1). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. Further, the refractory nature of cancer to drugs is well known in the art. Jain

(Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

In addition, anti-tumor agents and those that prevent, reduce, retard or eliminate secretion of metastatic promoters, must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor or metastatic promotor producing cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or

clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established.

Cancer treatment in the current state of art is not a trivial matter as the above numerous cited references indicate. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed method in treatment of any cancer with a reasonable expectation of success. It is concluded that undue experimentation involving phase I, II, and III human clinical trials is required in order to practice the instant invention.

Claims 20-34 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to method of treating cachexia using autologous urine isolate as the main ingredient. However, the specification does not teach any enabling method of treating cachexia using autologous urine isolate. The specification does not teach any effective dose of autologous urine isolate to accomplish the purpose stated in the preamble of the claims. As summarized above, all of the examples in the instant specification use autologous APCs (i.e. autologous dendritic cells) treated with autologous urine isolates. Example 7 shows an antecdote treating cachexia using autologous urine isolate treated dendritic cells and Example 16 says that cachexia in a patient with AIDS can be treated with the HIU alone but do not say cachexia was treated. One cannot extrapolate the teachings of the specification to

the claimed invention because the specification does not teach any method of treating cachexia using autologous urine isolate of various sizes listed in the instant claims. As summarized above, all of the examples in the instant specification use autologous APCs (i.e. autologous dendritic cells) treated with autologous urine isolates. In addition, Younes et al (2000, Rev Hosp Clin Fac Med Sao Paulo 2000 Sep-Oct;55(5):181-93) review that cachexia is a complex problem involving abnormalies in many aspects of metabolisms in a body and difficult to treat. Further, Cariuk et al (IDS, 1997, British Journal of Cancer 76, pages 606-613) teach giving tumor antigens found in urine of cancer patients to mice causes cachexia in the mice. Note the abstract and the last paragraph of the article. Cachexia treatment is not a trivial matter.

Since the above cited review article indicates that cachexia is multi-faceted, complex problem that cannot be treated with imunogen alone, and the contradictory teachings of Cariuk et al, i.e. cancer antigen found in urine causes cachexia instead of helping to gain weight, and the specification provides insufficient guidance and provides no working examples (other than an anecdote with dendritic cells) which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed method in treatment of cachexia with a reasonable expectation of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

drop

Claims 1, 2, 6, 7, 16, 17, 19, and 70-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eldor (1997, Medical Hypothesis 48, pages 309-315) in view of Voet et al (1990, Biochemistry, John Wiley & Sons, page 682).

The claims are interpreted to drawn to cancer treatment using urine-derived antigen vaccination. Eldor reviews the literature data that teach various tumor antigens have been found in urines of cancer patents. Eldor further teaches the antigen found in urine could be used in cancer treatment (see the title, abstract, page 309 left column). Although Eldor does not specifically teach that use of urine isolate larger than 1,000 daltons for the cancer therapy, one in ordinary skill would know that urine contains toxic waste product such as urea whose molecular weight is less than 1,000 daltons (see the biochemistry text book by Voet et al, 1990, Biochemistry, John Wiley & Sons, page 682). Eldor further teaches at pages 309 and 310, isolating various sizes of antigens found in urine by employing a commercially available filter cartridge or chromatography is trivial in the art. Eldor also teaches at page 301, left column that adjuvant of instant claims 17 and 19 has been used in cancer therapy. Since pros and cons of using autologous vs. allogenic urine isolate have not been known, it might be easier to start with autologous urine isolate because it minimize effort of finding urine donor and Eldor teaches urine found in cancer patient contain useful antigens with carbohydrates and other modifications (see page 309, left column, line 9), it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use autologous urine isolated vaccine to test effectiveness of the vaccine especially in patients who have failed standard FDA approved therapies.

Claims 3-5, 8-15, and 70-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eldor (1997, Medical Hypothesis 48, pages 309-315) in view of Voet et al (1990, Biochemistry, John Wiley & Sons, page 682) as applied to claims 1, 2, 6, 7 above, and further in view of Nestle et al (IDS, March 1998, Nature Medicine, vol. 4, pages 328-332), and Zitvogel et al (IDS, 1998, Nature Medicine, vol. 4, pages 594-600).

The claims are drawn to cancer treatment by vaccination of urine-derived proteins of various sizes using various vaccination routes and the cancer treatment further comprises vaccination with autologous urine isolate-pulsed dendritic cells or exosomes derived from said dendritic cells. Nestle et al teach at page 328 right column, first paragraph that vaccination with diverse protein population diminish the chances of immune escape in a given patient and further teach that various administration routes of

the instant claim 3 including intralymphatic injection has been well known in the art before the effective filing date of instant application. Nestle et al further teach dendritic cells pulsed with a pool of tumor lysates (see page 332, left column under Methods section). Since Eldor teaches that various tumor antigens are found in urine of cancer patients, one in ordinary skill in the art would recognize that urine-derived tumor antigens may substitute the tumor-derived lysate, especially in patients that resection of tumor is not readily feasible option. Further, Zitvogel et al throughout the entire article teach that exosomes isolated from tumor-antigen pulsed dendritic cells are effective in treating tumors. Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to test if adding dendritic cells pulsed with tumor antigens found in urine of cancer patients, and/ or exosomes from said dendritic cells have better immune boosting effect, especially in patients who have failed the standard, FDA-approved therapies because these patient have nothing to loose from trying anything.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eldor (1997, Medical Hypothesis 48, pages 309-315) in view of Voet et al (1990, Biochemistry, John Wiley & Sons, page 682) as applied to claim 16 above, and further in view of Yedavelli et al (IDS, International Journal of Molecular Medicine vol. 4 pages 243-248. Yedavelli et al teach that a heat shock protein can be used as an adjuvant in cancer vaccination.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-

305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
October 31, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800
1600